Complete Summary

GUIDELINE TITLE

Iron.

BIBLIOGRAPHIC SOURCE(S)

Roger S. Iron. Nephrology 2006 Apr;11(S1):S217-29.

Roger S. Iron. Westmead NSW (Australia): CARI - Caring for Australasians with Renal Impairment; 2005 Aug. 24 p. [58 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Chronic kidney diseases
- Chronic dialysis

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Nephrology
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide advice on the assessment of iron stores and availability; guide the monitoring of iron stores and availability during the correction and maintenance phases of anaemia correction with epoetin; and outline the different iron preparations, optimal methods of administration and risks/side-effects associated with their use

TARGET POPULATION

Adults and children with chronic kidney disease and on chronic dialysis

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment

Iron stores and availability prior to and after commencement of erythropoietic stimulating proteins (epoetin)

- Serum ferritin
- Transferrin saturation
- Percentage of hypochromic red cells

Treatment*

1. Erythropoietic stimulating proteins
2. Iron supplementation

- Oral ferrous salts
- Intravenous iron

*Considered but not recommended

MAJOR OUTCOMES CONSIDERED

- Iron deficiency
- Iron overload
- Anemia

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Databases searched: MeSH terms and text words for iron stores were combined using 'and' with MeSH terms and text words for diagnostic accuracy and diagnostic measures. These were them combined using 'and' with MeSH terms and text words for iron supplementation. The search was carried out in Medline (1966 – November Week 3, 2003). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 25 November 2003.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Level I: Evidence obtained from a systematic review of all relevant randomized controlled trials (RCTs)

Level II: Evidence obtained from at least one properly designed RCT

Level III: Evidence obtained from well-designed pseudo-randomized controlled trials (alternate allocation or some other method); comparative studies with concurrent controls and allocation not randomized, cohort studies, case-control studies, interrupted time series with a control group; comparative studies with

historical control, two or more single arm studies, interrupted time series without a parallel control group

Level IV: Evidence obtained from case series, either post-test or pretest/post-test

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The cost benefit of intravenous iron supplementation in patients treated with epoetin was considered. Currently, there are no Australian studies looking at this important issue. In the United Kingdom, intravenous (IV) iron supplementation in patients with both absolute iron deficiency, and those with a serum ferritin > 100 µg/L, showed a 33% reduction in epoetin dose following regular low dose IV iron gluconate.

The cost of pushing iron stores and iron availability above 'normal' values may have to be revisited in the context of more expensive IV iron preparations, oral heme iron preparations, and the future accessibility of biosimilar epoetins.

METHOD OF GUIDELINE VALIDATION

Comparison with Guidelines from Other Groups
Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Recommendations of Others. Recommendations regarding blood pressure control targets in chronic kidney disease from the following groups were discussed: Kidney Disease Outcomes Quality Initiative, British Renal Association, Canadian

Society of Nephrology, and European Best Practice Guidelines (To Reach and Obtain Target Hb and Practical Recommended Minimum).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the levels of evidence (I–IV) can be found at the end of the "Major Recommendations" field.

Guidelines

Assessment of iron prior to and after commencement of synthetic erythropoietic

Stimulating proteins (referred to as epoetin):

a. Dialysis patients should have regular assessment of iron stores and availability, as iron deficiency is a common cause of anaemia within this population. (Level II evidence)
b. Chronic kidney disease (CKD) patients on dialysis should have sufficient iron stores to achieve and maintain haemoglobin of 110 g/L, with iron supplements being administered to maintain the recommended targets for iron status. (Level l evidence)
c. Prior to the commencement of epoetin, adequate iron stores should be ensured. The following indices of iron stores and availability should be maintained:
    - Serum ferritin > 100 µg/L
    - Transferrin saturation (TSAT) > 20%
    - Percentage of hypochromic red cells < 10% (Level II evidence)
d. Optimisation of epoetin dose may be obtained by achieving higher target values of iron storage than the levels that define absolute or relative iron deficiency:
    - Serum ferritin 200–500 µg/L
    - TSAT 30–40%
    - Percentage of hypochromic red cells < 2.5% (Level II evidence)

Suggestions for Clinical Care

(Suggestions are based on Level III and IV sources)

- Assessment of iron prior to and after commencement of synthetic erythropoietic stimulating proteins (referred to as epoetin):
    a. During the induction phase of epoetin therapy, there is a risk of developing functional iron deficiency in patients who had adequate iron stores (as defined above) at the beginning of treatment. Prescribers must be aware of this phenomenon and be willing to prescribe additional intravenous iron to overcome this barrier to epoetin resistance. (Level III evidence)
    b. In patients in whom serum ferritin is > 500 µg/L (or TSAT > 40%), intravenous iron should be withheld for up to 3 months as long as there are no signs of functional iron deficiency (percentage of

hypochromic red cells > 10%), at which time the iron parameters should be re-measured before intravenous iron is resumed. (Level III evidence)

c. When the serum ferritin has declined to < 500 µg/L (or TSAT < 40%) and/or the percentage of hypochromic red cells has increased to > 10%, intravenous iron can be resumed at a dose reduced by one half. (Level III evidence)

- Monitoring iron levels:

    a. Dialysis patients with stable haemoglobin not treated with epoetin, with ferritin > 100 µg/L and TSAT > 20%: three-monthly. (Level IV evidence)
    b. At initiation of epoetin therapy or during period of increased epoetin dose, whether or not intravenous iron is being given: monthly. (Level IV evidence)
    c. Following attainment of target haemoglobin: three-monthly. (Level IV evidence)
    d. Measurement of iron stores must be deferred for 1 week following an intravenous iron dose of < 200 mg iron polymaltose, or for two weeks if larger dosages are used (> 200 mg iron polymaltose). (Level IV evidence)

- Administration of iron:

    a. Supplementary iron should be administered to prevent iron deficiency and to maintain adequate iron stores, so that dialysis patients can achieve and maintain a haemoglobin concentration > 110 g/L, with or without epoetin therapy. (Level II evidence)
    b. Most patients will benefit from supplementary iron, especially during the correction phase of anaemia management. IV iron is the preferred route of administration as oral iron is poorly absorbed.
    c. Most patients in whom the serum ferritin concentration is > 500 µg/L, TSAT is > 30% and percentage of hypochromic red cells < 10% will achieve or exceed a haemoglobin concentration of 110 g/L with supplementary epoetin (note: TSAT is percentage of transferrin saturated with iron). (Level II evidence)

- The current Australian Medicare schedule benefit for iron monitoring can be requested as 'iron studies', (which includes percentage transferrin saturation and ferritin) or ferritin by itself. The increased cost of requesting iron studies is justified, so as to allow a broader assessment of iron status. The costs (2005) are $36.50 (iron studies) vs. $23.95 (ferritin) respectively.
- Haemodialysis (HD) units must be aware of possible variations in routine "monthly" blood testing, e.g., after the long break vs. midweek, as this may impact on the timing of measurement of iron status with respect to IV iron dosing.
- Achieving a target ferritin of 200–500 µg/L for the population will ensure that the majority of patients will have a ferritin > 100 µg/L.
- Following on from the revised European Best Practice Guidelines, being a reasonable compromise between possible enhancements of epoetin activity vs. the risks of iron overload, the suggested upper limit for ferritin is 800 µg/L. In a similar vein, without data support, IV iron should be withheld during concurrent bacterial infections.

Haemodialysis

- There is no indication for oral iron in HD patients. Supplementary iron should be administered intravenously.
- Most patients on HD will require repetitive dosing of intravenous iron to achieve and maintain a haemoglobin concentration > 110 g/L. Intravenous iron (iron polymaltose) can be administered as either a 100 mg dose/week or as a 500–1000 mg bolus dose.

Peritoneal Dialysis

- Peritoneal dialysis (PD) patients can be given oral iron in the form of ferrous salts at a daily dose of 100–200 mg of elemental iron. Optimum absorption will occur if it is prescribed as a single dose at night without concomitant food or other medicines.
- Some PD patients, particularly if they are receiving epoetin, will not be able to maintain adequate iron stores with oral iron. Because of ease of administration, bolus dosages of intravenous iron are often prescribed. Intravenous iron should be administered slowly using veins that will not be used for HD vascular access.
- In the maintenance phase, oral iron can on occasion, sustain adequate iron stores to allow erythropoiesis to continue efficiently.

	Haemodialysis	**Peritoneal Dialysis**
Initiation of epoetin	IV	Oral $\pm$ IV
Maintenance of epoetin	IV	Oral $\pm$ IV

Definitions:

Levels of Evidence

Level I: Evidence obtained from a systematic review of all relevant randomized controlled trials (RCTs)

Level II: Evidence obtained from at least one properly designed RCT

Level III: Evidence obtained from well-designed pseudo-randomized controlled trials (alternate allocation or some other method); comparative studies with concurrent controls and allocation not randomized, cohort studies, case-control studies, interrupted time series with a control group; comparative studies with historical control, two or more single arm studies, interrupted time series without a parallel control group

Level IV: Evidence obtained from case series, either post-test or pretest/post-test

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of iron levels in patients with chronic kidney disease

POTENTIAL HARMS

- During the induction phase of epoetin therapy, there is a risk of developing functional iron deficiency in patients who had adequate iron stores at the beginning of treatment. Prescribers must be aware of this phenomenon and be willing to prescribe additional intravenous iron to overcome this barrier to epoetin resistance.
- Regular monitoring of iron status (at least every 6 months) is essential during treatment to avoid toxicity.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Passive dissemination of the Caring for Australasians with Renal Impairment (CARI) iron guideline has raised awareness of the guidelines but for iron management to improve in the clinical environment takes commitment to change within the renal team, an agreed iron protocol with a decision support aid, a working process for iron management and increased skills for renal nursing staff. Factors impacting the iron process and barriers to change are numerous. For implementation to succeed, a strategy that aims at overcoming these barriers in an individual unit should be planned and executed.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Apr

GUIDELINE DEVELOPER(S)

Caring for Australasians with Renal Impairment - Disease Specific Society

SOURCE(S) OF FUNDING

Industry-sponsored funding administered through Kidney Health Australia

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Author: Simon Roger

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All guideline writers are required to fill out a declaration of conflict of interest.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Caring for Australasians with Renal Impairment Web site.

Print copies: Available from Caring for Australasians with Renal Impairment, Locked Bag 4001, Centre for Kidney Research, Westmead NSW, Australia 2145

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- The CARI guidelines. A guide for writers. Caring for Australasians with Renal Impairment. 2006 May. 6 p.

Electronic copies: Available from the Caring for Australasians with Renal Impairment (CARI) Web site.

PATIENT RESOURCES

None available

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